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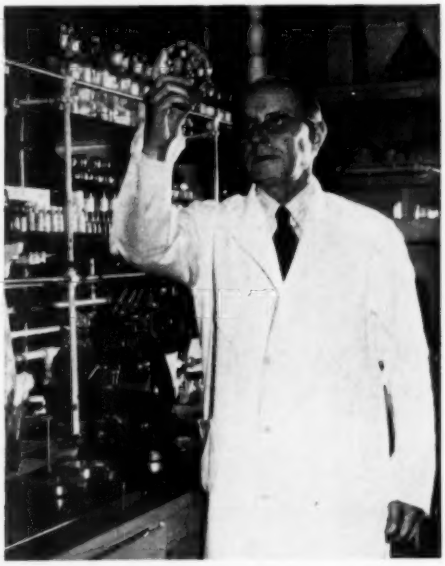

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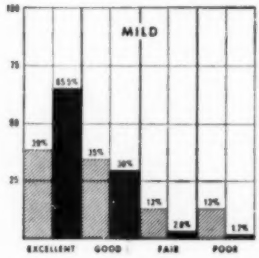
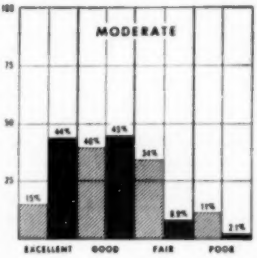
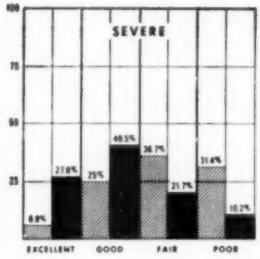
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

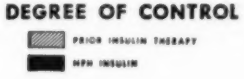
Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879









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OUR COVER

DR. BENJAMIN M. DUGGAR

DR. BENJAMIN M. DUGGAR, shown on the cover of this issue of the Journal in his laboratory at Pearl River, N. Y., is consultant in mycological research for Lederle Laboratories. It was he who discovered aureomycin, the golden antibiotic with such wonderful properties.

On March 25, 1953, Dr. Duggar received the Rho Chi Citation at the Philadelphia College of Pharmacy and Science, in compliance with the unanimous recommendation of the executive officers of Alpha Tau chapter of the Rho Chi Honorary Pharmaceutical Society. Following the presentation, he delivered the first annual Julius W. Sturmer Memorial Lecture in which he outlined the procedures necessary in the development of new antibiotics.

Dr. Duggar's stay in Philadelphia for this address was his final engagement in a two-week trip through the middle Atlantic States during which he delivered a number of lectures and collected numerous soil samples to be tested for possible antibiotic content. Three days after his appearance in Philadelphia, he was en route to Japan on a similar venture. To be with this marvelous scientist, who is now more than 80 years of age, and to hear his optimism and clear thinking about the future, was indeed inspirational.

EDITORIAL

RATIONAL PRACTICAL EXPERIENCE

THE arguments that have been advanced pro and con the practical experience requirement for pharmacy licensure would fill many volumes. The Pharmaceutical Survey passed its critical judgment on this question and recommended that "the present requirements for practical experience as to a prerequisite for licensure be modified to be of more practical value or else abolished."

Since this pointed criticism was voiced many boards of pharmacy have taken steps to upgrade the quality of practical experience. This has been done in various ways. Experience gained before enrollment in a college of pharmacy is not now generally credited. Time spent during the academic year is not approved by many states. A sizable number of boards require that some of the experience be gained after graduation from college. New Jersey has been the most exacting in this regard since this state requires a full year of pharmacy internship after college graduation. All of these innovations are sensible provisions which were long overdue. Several years ago it was common to have a freshman student enroll in college with all the experience requirements having been met. This would be analogous to a first year medical student having served his internship in the hospital before entering medical school!

Credit for experience gained while working at night during the college year was and still is a source of great difficulty since this encourages students to work while attending college. With the heavy and difficult pharmaceutical curriculum, working while attending college is likely to be disastrous for the average student. Neither is the student wise who so dissipates his time and energy on extracurricular activities or work that he makes only a passing grade. College is the time and place to acquire a superlative training in the sciences supporting pharmacy as well as its professional disciplines. Practical experience should be built on this and not allowed to interfere with it. The New Jersey plan is ideal in this respect since all practical experience must be obtained after the college training just as in medicine.

There are those who claim that the colleges should give or supervise practical experience. This is either impossible, or at the very least not feasible. Just as the medical intern in his hospital duties must actually meet and care for the sick and the injured to the pharmacy intern must learn to translate his college training into action on the site of operations, in the pharmacy. The model pharmacy on the college campus can never duplicate the actual working conditions in the retail store, the prescription pharmacy or the busy hospital pharmacy.

Should the college administrator attempt to supervise practical experience gained in stores off the campus he would be embracing a situation that would lead him into all sorts of unforeseen difficulties. This indeed is the responsibility and duty of the board of pharmacy; yet most board members shy away when it is suggested that they function more energetically in this respect.

Undoubtedly, practical experience can and should be of great value to the prospective pharmacist. It can be of value only when it is gained in those establishments where pharmacy is practiced on a proper professional plane and where the pharmacist-preceptor faces his teaching and training task with a sense of responsibility to both the intern and the profession. If interns are simply considered cheap help, given menial tasks to do, and no counsel nor advice they cannot be expected to gain much from this experience. In the final analysis, a newly registered pharmacist who is unfamiliar with the practical operations in a pharmacy is concrete evidence that some preceptor-pharmacist has failed to meet his obligations. Pharmacists who criticize these young pharmacists for a lack of practical knowledge should actually criticize their preceptors and possibly even a little critical self-examination is also in order. Boards can and should pass on the qualifications of both stores and pharmacists to train pharmacy interns and do this with courage and conviction. In their hands lies the solution to this problem.

L. F. Tice

RUTIN IN EUCALYPTUS SPECIES*

By C. F. Krewson, C. S. Fenske, Jr., J. F. Couch** and J. Naghski

IN our search for a domestic source of rutin other than tobacco, which has a low rutin content (0.5%) and is expensive, we examined many species of plants. Of these, buckwheat (*Fagopyrum spp.*) containing from 2 to 7% of rutin (2, 8, 9), *Sophora japonica*, containing from 13 to 23% (3), and *Eucalyptus macrorrhyncha* appeared to be the most promising sources. At present, all three are used commercially for the production of rutin.

We have examined the leaves of 21 species of *Eucalyptus* growing in California. Only one of the species, *E. macrorrhyncha* F. v. M., contained rutin. This specimen was a mature tree in Golden Gate Park, San Francisco, California.

Rutin was first reported in *E. macrorrhyncha* by J. H. Maiden (4) and later, in 1898, by Henry G. Smith (13, 14), who named it "myrticolorin", believing it was a new quercetin glycoside. It was pointed out by Schmidt in 1908 (12) that myrticolorin was probably identical with rutin, and this was later confirmed by Perkin (10). Rodwell (11) found 6.8 to 11% of rutin in the leaves of *E. Youmani* Blakely and McKie, a species not available to us for examination.

E. macrorrhyncha F. v. M. (1, 6), often spelled *macrorhyncha*, is native to Australia. It is described (1) as a small to medium-size tree with a characteristic stringy bark, which is persistent on the stems and large branches. Because of this characteristic, it is known as the "red stringybark" of New South Wales and the "ordinary stringybark" of Victoria. In Australia it is essentially a mountain species growing on comparatively sterile mountain ranges on white, acid, poor soil and on granite.

Although the eucalyptus are native to Australia, many species have been introduced into California, in locations with climatic and soil conditions similar to those of their native habitat. Concerning these

* Eastern Regional Research Laboratory, Philadelphia 18, Pennsylvania. One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

** Deceased.

cultivated specimens in the United States, McClatchie (5) states that ". . . the specimens growing in the Southwest do not yet give promise of attaining great size, due probably to being planted at too low an elevation". He continues, "The tree is a promising one for a forest cover for mountain ranges of the Southwest." Thus there exists the possibility that *E. macrorrhyncha* may be grown here as a domestic source of rutin. The feasibility will depend on the economics of harvesting the leaves and on the time required for the plants to be brought into production. Some data on the effect of age of the trees on the rutin content of their leaves are presented in this paper.

Experimental

The rutin and moisture contents were determined according to the method of Naghski et al. (7). Table I shows the rutin contents of leaves from young plants and those from a mature *E. macrorrhyncha* tree growing in the vicinity of San Francisco.

TABLE I

RUTIN CONTENT OF LEAVES FROM EUCALYPTUS MACRORRHYNCHA GROWN IN VICINITY OF SAN FRANCISCO, CALIFORNIA

Date Collected	Age of Trees, Months	Moisture, %	Rutin, % [a]
Oct. 1946	Mature tree	42.3	12.8
May 1948	6 [b]	64.6	2.1
Aug. 1948	9	67.4	11.9
Nov. 1948	12	64.0	8.1
Nov. 1948	14	6.8 [c]	9.6
Nov. 1948	14	6.7 [c]	10.2
Nov. 1948	14	6.0 [c]	9.0
Nov. 1948	14	7.0 [c]	9.4
June 1949	19	65.3	9.2
Oct. 1949	23	63.9	4.9

Except for the leaves from the seedlings grown in the greenhouse, and the one sample from 23-month-old plants collected in October, the rutin content of the leaves from young plants is almost as high as

[a] Moisture-free basis
[b] Grown in greenhouse
[c] Samples air-dried immediately after they were collected

that of the leaves from the mature tree. In Australia, Rodwell (11) observed that leaves from young regrowth from cut stumps contained only 2 to 5% of rutin and that leaves from coppice had a lower rutin content than those from mature trees in the same area.

Table II shows the rutin content of leaves from Australian *E. macrorrhyncha* received in three different years.

TABLE II

RUTIN CONTENT OF LEAVES OF EUCALYPTUS MACRORRHYNCHA OBTAINED FROM AUSTRALIA

Year Collected	Description [a]	Moisture, %	Rutin, % [b]
1946	Matured leaves from main branches	7.9	13.7
1946	Young leaves from main branches	8.4	23.1
1946	Leaves from young shoots	8.2	11.9
1947	Leaves and small twigs	8.2	8.0 [c]
1947	Leaves and twigs	12.1	8.0
1948	Leaves and twigs	8.5	7.7

The young leaves collected from main branches were exceptionally high in rutin, containing 23.1 percent whereas mature leaves contained only 13.7 percent. The low content of rutin of the sample obtained in 1947 and 1948 was due to the dilution effect of the twigs, which contained only small amounts of rutin. Analysis of a sample of young twigs showed 4.0% rutin, whereas none was found in mature material. Rodwell (11) observed a similar relationship between the age of the leaves and the rutin content. He also found that the youngest twigs contained about 6% rutin but that the content decreased as the stems matured.

In addition to *E. macrorrhyncha* the leaves of the following twenty species of *Eucalyptus*, collected from specimens growing on the campus of Stanford University, Palo Alto, California, were examined and found to contain no rutin:

E. baueriana Schau.
E. botryoides Sm.
E. cornuta Labill.
E. leucoxylon F. v. M.
E. paniculata Sm.
E. polyanthemos Schau.

[a] All samples air-dried
[b] Moisture free basis
[c] Sample analyzed by extraction with boiling water

E. corynocalyx F. v. M.
E. costata Br. aff.
E. crebra F. v. M.
E. eugenioides Sieb.
E. ficifolia F. v. M.
E. globulus Labill.
E. goniocalyx F. v. M.
E. robusta Sm.
E. rostrata Schl.
E. rudis Endl.
E. salmonophloia F. v. M.
E. sideroxylon Cunn.
E. tereticornis Sm.
E. viminalis Labill.

Rodwell (11) examined the following five other species and found no rutin:

E. dives
E. obliqua Messmate
E. capitellata Sm.
E. tinghaensis
E. muelleriana Howitt

Summary

Leaves from twenty-one species of *Eucalyptus* growing in California were examined for rutin. Only one, *Eucalyptus macrorrhyncha* F. v. M., contained rutin. The rutin content ranged from 2.1% in the leaves from seedlings to 23.1% in young leaves from a mature tree. The rutin content of leaves from one to two-year-old trees was comparable with that of the mixed leaves from mature trees.

Acknowledgments

The authors wish to thank the following for their assistance in securing the samples of *Eucalyptus* used in this investigation: F. DeEds, Western Regional Research Laboratory, Albany, California; M. W. Talbot, S. N. Wyckoff and N. T. Mirov, Forest Service, U. S. Department of Agriculture, Berkeley, California; H. A. Spoehr and D. D. Keck of the Division of Plant Biology, Carnegie Institution of Washington, Stanford University, California; J. L. Gerod, Office of the Park Commissioners, San Francisco, California; W. Hartley, Division of Plant Industry, and M. F. Day, Division of Economic Entomology, Council for Scientific and Industrial Research, Canberra, Australia.

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DOES PHARMACEUTICAL EDUCATION NEED A PUBLIC RELATIONS PROGRAM? *

By Dr. Robert L. Swain **

THE topic, "Does Pharmaceutical Education Need a Public Relations Program?" is both interesting and provocative. Interesting, because it raises a question with which pharmacy has been little concerned. Provocative, because it suggests that this lack of concern may not have been altogether justified or altogether sound.

In studying this question, I was impressed with the fact that while pharmaceutical education is by all odds pharmacy's most valuable asset, we have been far from astute in utilizing it for the progressive improvement of pharmacy's standing with the medical profession, the drug industry, and the general public.

If there is any one thing throughout the broad field of pharmacy which conforms to high academic and professional standards, it is our system of pharmaceutical education. It is the one segment of the pharmaceutical field which has progressively moved forward over the years, and which today reflects pharmacy in a truly professional manner.

Pharmaceutical education has become of age, fully matured, and represents that level of achievement which no other phase of pharmacy has reached. It can be said that it is in our colleges of pharmacy that the hopes and aspirations of the pharmaceutical profession have been realized.

It is because I believe these statements are absolutely true that I feel we have been remiss in not undertaking some plan or procedure for making the public aware of what pharmaceutical education is, its basic philosophy, and the objectives to which it is devoted.

It stands to reason, so it seems to me, that pharmacy can never expect to hold its proper position in public estimation until the public comes to understand and appreciate the professional educational foundation upon which pharmacy rests.

Stated differently, any worthwhile improvement in pharmacy's public relations must depend upon a more intelligent view of pharmaceutical education upon the part of the people generally.

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* Presented at Meeting of the Boards and Colleges of Pharmacy—District Number 2 Albany, New York—March 1, 2, 3, 1953.

** Editor, *Drug Topics*, Editor, *Drug Trade News*.

Let me cite here a few instances which have come to my attention which, so it would appear, show the utter necessity of giving the public a sounder view of the basic assets of pharmaceutical education.

Shortly after Christmas, 1952, a widely known radio and television performer made a statement which I think you will find worthy of your attention. On his highly popular television show, he had children as his guests, and he asked each of them what he intended to do when he grew up.

One lad, about 15 years old, said he was going to study pharmacy and become a pharmacist. This was greeted with this statement from the television personality: "Isn't it a shame that after graduating from a school of pharmacy, you will have no opportunity to practice what you have been taught?"

I have no doubt that this scene was witnessed by millions of people, and I have no doubt that the net effect of the incident was to give pharmacy a slap in the face and to diminish public respect for the profession as a whole.

If there is no place in which the graduates of our schools of pharmacy can utilize their professional and technical training, something must be basically wrong, and I should surmise that the public would come to this conclusion.

We know, of course, that the statement made to the prospective pharmacy student was uninformed, unintelligent, and completely unjustified, but even so, this statement was made to millions, and because of it, the questions which it raised, and the implications of them, cannot go unnoticed by pharmacy in general.

Some time ago, I had occasion to suggest a pharmacist for a technical position in the laboratory of a state health department. The head of these laboratories was a distinguished chemist. He held the degree of doctor of philosophy from Johns Hopkins University, and he was in every respect a truly eminent scientist.

When I suggested a pharmacist to him, he was inclined to treat my recommendation facetiously, as he doubted very much that a pharmacist would be found who merited his favorable consideration.

In the course of the conversation, he displayed a complete lack of understanding of pharmaceutical education, and was strongly inclined to deprecate the curriculum of the colleges of pharmacy. When I pressed him for some basis for his view, he admitted that he knew virtually nothing of the scope and content of a modern college of pharmacy curriculum.

I told him that he should withhold judgment until he knew what he was talking about, and that if he was willing to inform himself on the subject, I would give him the necessary factual information. This seemed fair enough, and I turned over to him the latest edition of the Pharmaceutical Syllabus, and asked him to study it at his leisure and to return the Syllabus to me when he finished with it.

He kept it for at least a month, and when he returned it to me, he expressed amazement that any such curriculum was in effect in the colleges of pharmacy. He said that it far outstepped the academic and scientific work done in the liberal arts college, and so far as he knew, went way beyond the training given students in any other four year period of undergraduate instruction. He apologized for his uninformed and somewhat reckless repudiation of pharmaceutical education, and said that he would be glad indeed to give the pharmacist I had recommended to him a place on his technical staff.

Not only did the pharmacist come up to his expectations in the quality of the scientific and technical work assigned to him, but he later moved on to still higher scientific and technical work in another agency and is a highly creditable example of what modern pharmaceutical education has to offer.

I mention this incident, because it serves to illustrate how seriously handicapped pharmacists are when it comes to participating in professional and scientific fields. If little or nothing is known of the pharmacist's professional and technical training, very little in the way of opportunity and recognition can be expected among professional and scientific people.

How does pharmaceutical education stand with the medical profession? A personal experience, I think, illustrates the point. I recently met with a group of people concerned with some of the problems of pharmaceutical education. Among these present was a distinguished medical scientist with whose professional career I was quite familiar.

During the course of our discussion, I made the comment that the teaching of pharmacology in many of our colleges of pharmacy was superior to that afforded by many schools of medicine. I suggested that the course of instruction was more inclusive and more representative of the field of current medication than that given in schools of medicine.

The medical scientist in question not only expressed his disbelief of what I said, but he declared that he would be surprised if any col-

lege of pharmacy gave worthwhile training in pharmacology. Not only was this his view, but he seemed to indicate that he felt the subject was one that had no place in pharmaceutical education, as it was primarily one for medicine, and the medical student.

Now, there can be no doubt that this is the overwhelming view of the medical profession, certainly insofar as pharmacology is concerned. They regard it as a subject exclusively within the province of medicine and thus entirely without the area of pharmaceutical education.

This is an important matter, as certainly pharmacists can never hope to enjoy that degree of confidence and respect of the medical profession to which they are richly entitled until physicians are familiar with the scope, depth and breadth of the pharmacy curriculum.

Indeed, it is my conviction that, by and large, physicians do not have any well conceived notion of what pharmacists are taught, and thus have no working knowledge of what pharmacists are qualified to do. This matter takes on a peculiar significance when we realize the strategic position which pharmacists should occupy with the physicians of their neighborhoods.

Physicians are finding it more and more difficult to keep up with modern prescription medication. In spite of the many medical journals, scientific articles and other media available to them, these are, by and large, given no more than a cursory look. It has been well established that physicians on the average, spend less than two hours per week in reading medical publications, medical books, and perusing other sources of medical information.

It is also established that there is a distinct tendency upon the part of physicians to rely upon pharmacists for information of this kind. This tendency would be vastly stimulated if physicians were more fully familiar with pharmaceutical education and with the advantages which it confers upon its graduates.

As the situation is shaping up, the opportunity for closer relationships with medicine is becoming brighter year by year. This being true, we should regard it as a duty to use this to our advantage, and one step in achieving this end is to make physicians more appreciative of the technical knowledge and professional skills which graduation from a modern college of pharmacy implies.

Just a few days ago, a representative of a manufacturer called upon me to discuss the feasibility of relying upon the pharmacist to aid in bringing facts regarding new prescription medication to physicians.

He said that while theoretically this would seem a desirable thing to attempt, actually, the manufacturer was skeptical as to the pharmacist's educational fitness to serve in this capacity.

Believe it or not, he had nothing approaching a sound conception of pharmaceutical education, and for this reason, was unable to view the pharmacist from the proper light and from the proper perspective.

I relate this incident to give further emphasis to my contention that while pharmaceutical education is our greatest asset, we have fallen far short of making this asset stand out in its true value. Indeed, we might well ask, how can we expect the drug industry fully to utilize the services and talents of pharmacists if they have no adequate conception of what these services can be and of what these talents are?

It is my conviction that, by and large, the public also knows very little about the intrinsic nature of pharmaceutical education. On a number of occasions, I have tried to ascertain just how the public feels about the college of pharmacy curriculum.

While most people with whom I have talked are aware that training of some kind is required, it is my opinion that they regard the pharmacy course largely from a trade school angle. Indeed, I have run into one instance where the impression seemed to be that the pharmacy student's training consisted of that offered by the ordinary business college, with some technical and pharmaceutical subjects tossed in to give it a phamaceutical flavor.

When viewed from the standpoint of the public, this subject becomes one of momentous significance. From a competitive standpoint, retail pharmacy is faced with a very drastic situation. There is a very perceptible drift of drug store merchandise into supermarkets, and into other non-drug mass distributors.

This drift has been due to the peculiar shopping advantages which the supermarket affords and also because, to the average consumer at least, drug store products are merely so many merchandise items.

This drift has also been influenced somewhat, and perhaps largely, by the fact that the average consumer is not aware of any reason why she should refrain from purchasing drug store products in supermarkets and confine her purchases of these products to the drug store.

This does not mean that consumers are unaware of the pharmacist's prescription services, but it does mean that they have not

been sufficiently informed of the pharmacist's professional function in the distribution of what we might term over-all drug store merchandise.

For this reason, they have manifested a willingness to rely upon non-drug outlets for many items, articles and products which we firmly believe should be very closely identified with the drug store.

In the light of this phase of our problem, it seems to me highly imperative that serious thought be given to ways and means of making the public more fully aware of the basic character of pharmaceutical education, as it is from this knowledge that the public will come to a sounder appreciation of pharmacy and a better grasp of the pharmacist's place in community life.

It is my conviction that if the public could visualize the pharmacist and the drug store in terms of an adequate understanding of pharmaceutical education, the pharmacist and the drug store would surely attain a stronger place in public estimation.

From these observations, it might be assumed that I regard pharmaceutical education as the keystone of the pharmaceutical arch, and as the one most promising approach to an improvement of pharmacy's relations with the public.

This is, indeed, my deep-seated conviction, as I see little chance of meeting pharmacy's professional needs and strengthening its competitive position until the public fully appreciates what the pharmacist is and comes to a sure-footed understanding of the significance of the drug store to community life.

All of which means that we should be astute enough to develop some practical program for educating the medical profession, the drug industry, and the public at large to the fundamental merit of pharmaceutical education.

It is our most priceless asset, and one which we should be intelligent enough to put to the best advantage. How is this to be done? Obviously, this does not admit of a yes or no answer. At the outset, we should disabuse our minds that public relations, as that term has come to be used, has any special significance to us.

I don't have in mind a public relations counsellor nor a publicity program such as the term "public relations" connotes in so many minds. I am merely suggesting that we make the best possible use of the opportunities within our reach. The deans of our colleges of pharmacy, and the members of our pharmacy teaching staffs, could

do much if they were to see to it that pharmacy is properly presented to the colleges of medicine and medical students.

While I don't claim to have any blueprint as to how this could be accomplished within the usual university administration, I am sure that if pharmacy deans and their faculty colleagues were to devote themselves to this project, much good would result.

By this I don't mean to imply that our pharmacy deans and faculty members are unmindful of this problem. I am merely trying to indicate that greater efforts should be made in this direction.

I would suggest, too, that drug industry leaders be asked to visit colleges of pharmacy to converse with the deans and faculty members with respect to their aims, purposes and fundamental philosophy so that the manufacturing segment of pharmacy might have a sounder appreciation of pharmaceutical education which, when properly understood, must be looked upon as the foundation of the whole pharmaceutical edifice.

Systematic efforts should also be made to make the public more aware of pharmacists' educational qualifications. Progress toward this achievement will come from having our educators appear before civic clubs, women's clubs, and other approaches to public opinion.

Vocational guidance counsellors and high school principals should be acutely aware of what pharmaceutical education is, and the opportunities which the modern pharmacist faces. I should like also to see well written, readable and definitive articles appear in some of our great consumer publications. These publications reach millions, and if their interest could be elicited, the impact of such articles would be beyond calculation.

In conclusion, and by way of summary, let me restate my honest conviction that the chief factor in improving pharmacy's public relations lies in giving the public a clearer appreciation of modern pharmaceutical education, and in bringing the medical profession and the drug industry into a closer relationship with our educational purposes and objectives.

I have no doubt, in the least, that pharmacy's professional prestige and its competitive position would progressively advance if some practical and workable means could be devised for making pharmaceutical education stand out as the reflection of pharmaceutical practice, and thus give the pharmacist and the drug store that position in public estimation which we know it richly merits and deserves.

THE BACTERICIDAL EFFICIENCY OF HELIOGEN *

By Louis Gershenfeld † and Bernard Witlin ‡

HELIOGEN obtained on the open market as tablets, wrapped individually in aluminum foil, is compounded with specially processed Chloramine-T, potassium iodide and other selected inorganic and organic materials. Each tablet dissolved in water "reacts to liberate 25 milligrams of free iodine."

In 1949, Ryan et al. (1) presented a clinical evaluation of this product in a properly controlled investigative study on wound therapy. They concluded that "(1) Heliogen, under the conditions used in this study, is not toxic, (2) it is successful in clearing up the odor and discharge of infected wounds with free drainage; and (3) wounds, including those chronically infected which had remained static under various therapies, responded favorably to Heliogen." They suggested that "Heliogen may prove to be a valuable addition to the chemotherapeutic agents used in the treatment of wounds." Since this report, various *in vivo* and *in vitro* studies have been carried out.

The first field of wide application and clinical usefulness has been for the treatment of oral affections. The clinical results here can be briefly reported by the comments as expressed by Berliner (2): "The effectiveness of one new preparation (Heliogen) merits special comment . . . controlled experiments were conducted . . . Although the investigation at the time of this writing has extended over a period of only eight months, on 117 patients, results have been most gratifying . . . The implications of this new preparation may well point the way to a multiplicity of potential uses."

In Ryan's presentation, mention is made that toxicity studies by the Department of Therapeutics of the New York University College of Medicine indicated that Heliogen preparations possessed a low toxicity. The statement also is made that "bactericidal tests *in vitro* have shown that Heliogen is effective in killing a wide variety of

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micro-organisms." However specific references concerning these *in vitro* findings were not given as in the case of the toxicity studies. It was with this thought in mind that we conducted this investigation to determine the effectiveness of Heliogen against different micro-organisms, especially against those concerned in the present primary clinical application of Heliogen.

Experimental

I. Free Iodine Content

Four Heliogen tablets were dissolved in 500 ml. of distilled water and assayed for free iodine with sodium thiosulfate (as given in the U. S. P. (3)). The free iodine content was 25.1 milligrams in each Heliogen tablet. Similar findings were obtained on four assays, each of different batches.

II. Bactericidal Efficiency Tests

(A) *Test Organisms:*

The test organisms employed were 24 hour-old liquid cultures, having been transplanted for at least six successive days prior to use. The organisms selected were either known strains of bacteria used in the testing of disinfectants or microorganisms apt to be found in the oral cavity or in the vaginal tract. The *Micrococcus pyogenes* var. *aureus* 209 and *Salmonella typhosa* Hopkins were obtained from the Food and Drug Administration and displayed the required resistance against phenol (4). The *Corynebacterium diphtheriae* was obtained from the Laboratories of the Health Department, City of Philadelphia. The *D. pneumoniae Type III* was obtained from the Laboratories of the National Drug Company. The *Monilia albicans* and a species of *Fusiformis* (isolated from the mouth) were obtained from the Caries Control Laboratory of the Dental School, University of Pennsylvania.

Escherichia coli, Klebsiella pneumoniae and *Streptococcus hemolyticus* were obtained from the stock cultures of the Department of Bacteriology, Philadelphia College of Pharmacy and Science.

Daily transplants of the *Micrococcus pyogenes* var. *aureus* 209, *Salmonella typhosa* Hopkins and *Escherichia coli* were made in 10 ml. F. D. A. broth (4). All of the other test organisms were cultured in 10 ml. Thioglycollate Broth U. S. P. (3).

(B) *General Procedure:*

One Heliogen tablet was dissolved in a designated volume of distilled water contained in sterile erlenmeyer flasks which were in a water bath adjusted to the designated temperature. An inoculum (volume noted below) of a 24 hour-old culture of the test organism was added to each flask containing the Heliogen Solution. At time intervals of 10, 20, 30, 45, 60, 90, 120, 180, 240 and 300 seconds, one standard loopful (4) and 0.1 ml. of the Heliogen-bacteria mixture were transplanted separately into 10 ml. of F. D. A. broth containing 1 percent sodium thiosulfate. In another series, the entire contents (60 ml.) in each flask * were separately transplanted into 60 ml. of double strength (2X) broth containing 2 percent sodium thiosulfate.**

HELIOGEN SOLUTION

(1) Inasmuch as Heliogen is recommended for use either as one or two tablets dissolved in four fluidounces (120 ml.) of water, a concentration of one tablet dissolved in 60 ml. of sterile distilled water was used in these tests. Employing the general procedure (see above), each tablet was dissolved separately in 60 ml. of sterile distilled water contained in individual sterile erlenmeyer flasks, each separately at temperatures of 20° C. (room temperature), 37° C. (body temperature) and also at 50° C. (the upper limit of what might be considered warm for water to be used in the mouth). All solutions were tested immediately.

Findings

In all instances, one tablet dissolved in 60 ml. of sterile distilled water killed separately on contact within 10 seconds the bacteria in a

* The "total swirl" technic was conducted because this technic is a more critical test method than the loop technique for many chemical compounds purported to possess germicidal properties and "is capable of measuring 100 percent kill" (5). Actually in this study if we limited ourselves to the conventional 4 mm. loopful transfer of the disinfectant-bacteria culture, the results would reveal that Heliogen Solution is effective in greater dilutions. Certainly the observation of a complete kill of 0.1 ml. and even more so of so large a number as present in 0.5 ml. of cultures of the test organisms are more critical tests than the loop technique to note the killing of the test organisms.

** F. D. A. broth (4) containing a final concentration of 1% sodium thiosulfate as an inactivator of free iodine was employed for *M. pyogenes* var. *aureus*, *S. typhosa* and *E. coli*. Thioglycollate Broth U. S. P. was employed in the tests with *Streptococcus hemolyticus*, *D. pneumoniae Type III*, *C. diphtheriae*, *Klebsiella pneumoniae*, a species of *Fusiformis* and *Monilia albicans*.

4 mm. loopful (4), 0.1 ml. and 0.5 ml. respectively inocula of *M. pyogenes* var. *aureus* 209, *S. typhosa* Hopkins, *E. coli, Strep. hemolyticus, D. pneumoniae Type III, C. diphtheriae, Klebsiella pneumoniae,* species of *Fusiformis* and *Monilia albicans.*

(2) It also is recommended that the solution prepared by dissolving the Heliogen tablet in water "should be used in successive rinses and gargles" and that "at least one minute should be devoted to this." A study therefore was made of the volume of solution which could be comfortably retained in the mouth. It was noted that the average amount of solution comfortably held by a person varied between 20 and 30 ml. The tests were repeated as above with 0.5 and 0.1 ml. inoculum of the above mentioned test organisms, using separately 30 ml. and 20 ml. quantities of the solution, made by dissolving one tablet in 60 ml. of distilled water.

Findings

In all instances 20 ml. and 30 ml. quantities of solution prepared by dissolving one Heliogen tablet in 60 ml. distilled water killed separately on contact within 10 seconds a 4 mm. loopful (4), 0.1 and 0.5 ml. inocula of *M. pyogenes* var. *aureus* 209, *S. typhosa, E. coli, Strep. hemolyticus, D. pneumoniae Type III, C. diphtheriae, Klebsiella pneumoniae,* species of *Fusiformis* and *Monilia albicans.*

Summary and Conclusions

(1) Heliogen tablets tested by the U. S. P. assay method for free iodine with sodium thiosulfate V. S. were found to contain 25.1 mg. of free iodine in each tablet.

(2) The bactericidal efficiency of a solution prepared by dissolving one Heliogen tablet in 60 ml. of sterile distilled water at either 20° C., 37° C. or 50° C. was adequate to kill separately on contact within 10 seconds the bacteria in a 4 mm. loopful, 0.1 ml. or 0.5 ml. inocula of the following 24 hour-old cultures: *Micrococcus pyogenes* var. *aureus (Staphylococcus aureus)* (4), *Salmonella typhosa* (typhoid bacillus) Hopkins (4), *Escherichia coli, Streptococcus hemolyticus, Diplococcus pneumoniae Type III* (pneumococcus),*Corynebacterium diphtheriae* (diphtheria bacillus), *Klebsiella*

pneumoniae (Friedlander bacillus), species of *Fusiformis* and *Monilia albicans.*

(3) Twenty ml. and 30 ml. portions of a solution prepared by dissolving one Heliogen tablet in 60 ml. of distilled water also killed the bacteria in a 4 mm. loopful, 0.1 and 0.5 ml. of 24 hour-old cultures of the test organisms (mentioned above) upon contact within 10 seconds, at either 20° C., 37° C. or 50° C. The 20 or 30 ml. portions are amounts comfortably retained in the mouth during rinsing or gargling.

(4) The conventional 4 mm. loopful transfer used in testing disinfectants revealed that Heliogen is an effective antibacterial agent even in weak dilutions. The techniques used in this study are more critical tests to note the killing of the test organisms. Here too, Heliogen in the concentration indicated above revealed bactericidal efficiencies against the many test organisms, which are of a resistance comparable to those pathogenic microorganisms found in the oral cavity and in the vaginal tract.

(5) Additional studies and an evaluation of the efficiency of Heliogen as compared with other products will be published at a later date.

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One Heliogen tablet was dissolved in 60 ml. sterile distilled water separately at three different temperatures, 20° C., 37° C. and at 50° C. and the solution in each instance was kept in a water bath at each of the designated temperatures. An inoculum (see general procedure) of a 24 hour-old culture of each of the test organisms was added to each flask containing the Heliogen solution. At designated time intervals, various amounts including finally the entire contents, (60 ml. in each flask), of the Heliogen-bacteria mixture were transplanted into media containing a final concentration of 1 per cent thiosulfate. After incubation, *in all instances* the findings were as recorded herein.

Time in Seconds	*M. pyogenes* var. *aureus* 209	*S. typhosa* Hopkins	*E. coli*	*Strep. hemolyticus*	*D. pneumoniae Type III*	*Klebsiella pneumoniae*	Species of *Fusiformis*	*Monilia albicans*
10	—	—	—	—	—	—	—	—
20	—	—	—	—	—	—	—	—
30	—	—	—	—	—	—	—	—
45	—	—	—	—	—	—	—	—
60	—	—	—	—	—	—	—	—
90	—	—	—	—	—	—	—	—
120	—	—	—	—	—	—	—	—
180	—	—	—	—	—	—	—	—
240	—	—	—	—	—	—	—	—
300	—	—	—	—	—	—	—	—
Control *	+	+	+	+	+	+	+	+

— = No growth after one week's incubation at 37° C.

\+ = Growth after one week's incubation at 37° C.

* = Controls were 60 ml. of sterile distilled water, treated in a manner identical to the 60 ml. Heliogen Solution throughout the test.

A HISTORY AND EVOLUTION OF THE SUPPOSITORY MOLD

By George Griffenhagen *

"THOU shalt reduce lion-skin, mix with lion-fat; let it dry, mix with cedar oil, make a suppository, put it to his anus."

Thus we have recorded one of the earliest prescriptions for the compounding of a suppository, translated from an early Assyrian medical clay tablet (ca 2600 B. C.) (1). Many prescriptions for suppositories may also be found in the early Egyptian medical papyri. Vaginal suppositories were also recommended such as this one translated from the Papyrus Ebers (1550 B. C.): (2)

"Fennel, Incense, Garlic, sert juice, Fresh Salt, Wasp's Dung. Make into a ball and put in the Vagina to cause a woman to deliver."

Hippocrates recommended the use of suppositories, calling them "Prosdita" or "Balanoi;" (3) while Paul of Aegina, the Byzantine physician, utilized a suppository of Hellebore "wrapped round or bound with some wool firmly" as a purge. His recommendations were that, "the head of this ball of wool is to be allowed to hang out of the anus, in order that after sufficient purging it may be in our power to remove the suppository" (4).

The word suppository comes from the Latin word "sub-ponere" meaning to place under, but there are some who feel that it means "substitute" in that suppositories were substitutes for an enema (5). The term pessary (vaginal suppository) comes from the Greek word describing a small stone for playing the game of draughts; while bougie (urethral suppository) comes from the French word meaning wax candle (6).

The suppository was a fairly common form of medication in the seventeenth and eighteenth centuries. William Salmon in the *New London Dispensatory* of 1691 lists formulas for nine suppositories and three pessaries. The base or binder recommended was either "boyled honey" or "the white of an egg and juice of Plantane" Other suppository bases which were in use during this period were wax, suet, lard, and soap. However, it was not until the introduction of cacao butter (oil of theobroma) that suppositories really gained complete acceptance by the medical profession.

The use of cacao butter for the preparation of suppositories can be traced back to the beginning of the 18th Century shortly after

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Homberg had isolated the "oil of theobroma"; and as early as 1766, Antoine Baumé (7) described the use of a suppository mold into which the liquefied cacao butter could be poured.

It was Alfred B. Taylor, pharmacist of Philadelphia, who popularized the use of cacao butter in America through an article in the *American Journal of Pharmacy* in 1852 (8). Taylor noted that the use of cacao butter in suppositories probably had its origin with the French, and it appears that Dr. Silas W. Mitchell, who was studying in Paris in 1851, brought the formula back with him. However, Griffith's *Universal Formulary* for 1850 had published the formula for a suppository of Hemlock consisting of "one part of white wax with four parts of butter of cacao" (9).

The new innovation was immediately accepted by a large section of the medical profession in America. Ellis' *Medical Formulary* for 1846 listed only one suppository (Soap and Opium) with no comments, while the very next edition in 1854 contained an entire section on the use and preparation of suppositories (10). Nine suppositories became official in the U. S. P. V, all utilizing cacao butter (11).

The use of this new material also brought about a change in the methods of compounding suppositories. Taylor had recommended the fusion method for preparing cacao butter suppositories in his original article. According to this method, the medicinal portion is mixed with a small amount of cacao butter and then added to the remainder of the previously melted cacao butter. After mixing thoroughly, the mixture should be poured into suitable molds. According to Taylor, "moulds should be made of sized paper and may be conveniently placed in a shallow box of sand to preserve their position" (12). Wiegand later gave exact instructions on the preparation of these paper molds. "A piece of glazed paper, not too thick is cut into oblong pieces, 2¼ inches long by 1½ inches wide and rolled into a cone, which should be ½ inch at the base and 1⅝ inches long. The free end of the paper is secured by a tip of sealing wax" (13).

The first metallic suppository molds in American were made by syringe manufacturers commencing about 1860 (14). They consisted of "a tin tray with a movable top perforated with a convenient number of holes; into these are put the individual moulds which are made of Britannia ware; the tray is filled with ice and the melted ingredients are poured into the moulds" (15). William B. Chapman, a Cincinnati pharmacist constructed one of the first molds made directly in a solid metal block. He made these molds in 1864-65, selling them to fellow pharmacists for $5.00 each (16). (See Illustration No. 1.)

Both of these molds presented the problem of removing the suppository from the mold after it had hardened. Probably the first suppository mold to be divided for easy removal of the suppository was manufactured and sold by Charles Bullock and Edmund Crenshaw of Philadelphia in 1867. It was hinged at the bottom and was described as "A series of moulds on two plates coming together, as in an ordinary bullet-mould" (17). Henry B. Brady of Newcastle-on-Tyne, England, produced a magnificently-machined mold prior to 1871 which was similar to the Bullock and Crenshaw mold. It was made of gun-metal plated with silver, and was sold to a few prosperous pharmacists for $125.00 each (18).

During the early 1870's the United States Patent Office granted patents on a variety of suppository molds, and by 1875 there were no less than nineteen varieties to be found on the market (19). Just to mention a few of the more widely used models, there was the Plaisted, a non-hinged, divided mold held together with a rubber band; the Blackman, a non-hinged, disc shaped, horizontally divided mold; the Benton, Myers and Canfield (Spenzer), the first end-hinged mold with a locking bolt; and the See (Maris), a circular mold with a central core, perpendicularly divided. Of these, Remington (20) recommended the Blackman as the best divided mold available, while Mat-

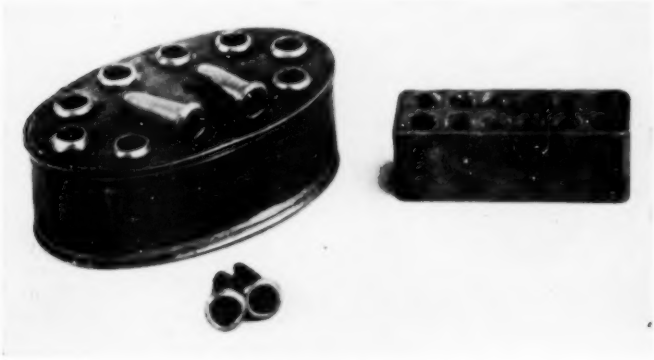

ILLUSTRATION No. 1

The first suppository molds to be manufactured in America are pictured here. The oval dish type mold on the left was marketed by syringe manufacturers as early as 1860, while the mold on the right was made by William Chapman of Cincinnati, Ohio, in 1864. (Photograph courtesy of Smithsonian Institution.)

tison (21) praised the Benton, Myers and Canfield mold as the best on the market. (See Illustration No. 2).

The fusion method of preparation of suppositories was not always suitable, and thus was by no means universally accepted by the pharmaceutical profession. Many preferred the hand molding method using a pill-tile, a rubber spatula and a little "secundum artem" (22). Thus the next step in the evolution of the suppository was the perfection of a "cold compression" mold which would compress the cacao butter into the desired size and shape without the necessity of using heat.

As early as 1868, Alexander M. Knowlson of Troy, New York, produced a "cold compression" suppository mold which was patented by the United States Patent Office (23). According to the inventor's specifications it consisted of a mold attached to a receiving-tube and plunger operating within the tube to force the suppository mass into the mold. George W. Sloan of Indianapolis, Indiana, also claimed to have invented a "cold compression" mold in 1875 which resembled an ordinary syringe (24) but Knowlson claimed a patent infringement, and the mold was probably never marketed (25). Emlen Painter of San Francisco, California, devised a simple compression mold in 1878

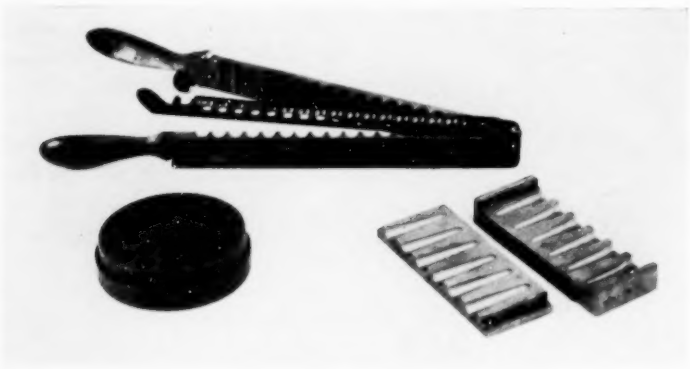

ILLUSTRATION No. 2

These three suppository molds are all original United States Patent models dating from 1873 to 1874. The lower left circular mold was patented by Lyman Blackman; the lower right mold by James Plaisted; and the long hinged mold by Peter Spenzer and assignee Benton, Myers and Canfield. They are all early examples of the divided suppository mold. (Photograph courtesy of Smithsonian Institution.)

similar to Remington's machine for compressing pills, whereby the compression was affected by striking the tamper with a mallet (*26*).

The first successful compression mold was patented by the inventor Henry R. Heyl of Philadelphia in April, 1879, and was introduced immediately to the profession by the assignee of the patent, Henry C. Archibald, pharmacist of the same city. The report by E. T. Ellis in the *American Journal of Pharmacy* announced the invention as "a machine which will revolutionize the present tedious and to some extent inaccurate way of preparing suppositories" (*27*). The machine consisted of a hopper in which is placed the mixture to be compressed; the plunger with hand lever for compression; the swing bed for holding the suppository mold; and the mold itself split longitudinally for easy removal of the suppository. (See Illustration No. 3.)

Improving on his original model, Henry C. Archibald with James F. Snediker of Philadelphia patented a second compression mold in 1891, which after additional improvements patented by Clarence W. Fox of Saugus, Massachusetts, in 1893, was manufactured and sold as the "Perfection" Suppository Mold by Fox, Foultz and Webster (*28*). Another rush to the United States Patent Office resulted in the granting of no less than eight different patents for compression type molds

ILLUSTRATION No. 3

This is the first successful "cold compression" suppository mold to be marketed. The model on the left is the original U. S. Patent Model which was submitted with the patent granted to Henry Heyl and assignee Henry Archibald in 1879. The one on the right is a cast iron commercial model of the same mold. (Photograph courtesy of Smithsonian Institution.)

in the 1890's (29). Of these, the Whitall, Tatum Mold which was patented by Charles A. Tatum of New York, in 1895, eventually replaced all other contemporary models. In 1897, Whitall, Tatum offered the mold for sale as their "No. 3 Suppository Machine . . . complete with nine molds," for $18.00 (30). The advantages which this mold seemed to offer were a large diameter wheel for easier application of compression, and a horizontal position with a large cylinder for a quantity of suppository mass.

Charles L. Trusler of Indianapolis, Indiana, patented the first powered suppository mold, complete with a cold water jacket surrounding the cylinder, in April, 1897 (31), and around 1900 Arthur Colton of Detroit, Michigan, offered for sale a similar power machine which according to their catalogue had a capacity for 1500 to 3000 cold compression suppositories every hour.

One of the first manufacturers in America to offer a complete line of suppositories to the profession was John Wyeth of Philadelphia. In 1882 he offered 66 different prepared suppositories for sale; and in 1886, he published a 20 page book exclusively on the subject for distribution to the profession (32). Henry S. Wellcome of Burroughs, Wellcome and Company, introduced a new double-cone shaped suppository in 1893 which he claimed offered better retention (33), and he purchased the patent rights to the Genese suppository mold. With the perfection of powered suppository machinery, a standard line of suppositories was added to the inventory of the majority of ethical pharmaceutical manufacturers.

The glycerin suppository was introduced in the U. S. P. in 1890, based upon the process which was perfected by Joseph P. Remington. An example of even more recent advances in the field of newer suppository bases is the use of propylene-glycol monostearate (Monolene). Here the release of medication is not dependent upon the melting point but on the hydrophillic properties of the suppository base. Other materials which have recently been proposed as suppository bases are hydrogenated peanut oil, cocoanut stearin, combinations of spermaceti and olive oil, and polyethylene glycols (Carbowaxes) (34). Gross and Becker (35) have presented the best review of recent literature on suppository bases to date.

Today there is considerable interest in the study of newer suppository bases, and as Gross and Becker have stated, "the old idea that a suppository base should melt at body temperature may become obsolete." As the newer suppository bases are proven, and cor-

responding new suppository molds are perfected, the ingenuity of those inventors of the profession who carried the evolution of the suppository from lion-fat to cacao-butter, and the evolution of the suppository mold from paper cones to powered compression molds, should be used as examples and guide posts to the future.

This brief history may also be of some value to those pharmacists who have preserved some of the relics of the past, and find one or more early suppository molds in their collection. For those who have the opportunity to visit Washington, D. C., the Division of Medicine and Public Health of the United States National Museum has placed upon exhibition more than a dozen of these early suppository molds herein described.

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(19) Mattison, R. V., *Ibid, 23*, 625 (1875).

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(21) United States Patents issued for suppository molds from 1871-1875:
Joseph P. Robbins of Medford, Mass., March 14, 1871, No. 112,634;
Lyman R. Blackman of Newport, R. I., June 17, 1873, No. 139,858;
Peter I. Spenzer of Cleveland, Ohio and assignor, Daniel Myers of same city, September 2, 1873, No. 142,524. Marketed as Benton, Myers and Canfield Mold;
James H. Plaisted of Waterville, Maine, January 20, 1874, No. 146,549;
Albert S. Wetmore of Cleveland, Ohio, and assignor Joseph E. Lavey of the same city, December 14, 1875, No. 170,975. This mold was also manufactured by Benton, Myers & Co. The See's suppository mold was not patented until February 17, 1880, No. 224,734, granted to James W. See of Hamilton, Ohio. It was manufactured by John M. Mario.

(22) Some very spirited arguments took place during the annual conventions of the American Pharmaceutical Association from 1870-1875. The pharmacists seemed to be about evenly split on the evaluation of the worth of the suppository mold.

(23) Knowlson, A. M., *Amer. J. Pharm. 47, 202* (1875). United States Patent issued to *Alexander M. Knowlson* of Troy, N. Y., July 14, 1868, No. 79,840.

(24) *New Remedies, 4, 270* (1875).

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(28) Remington, l.c. United States Patents issued to:
Henry C. Archibald and *James F. Snediker* both of Philadelphia, Pa., May 19, 1891, No. 452,743. *Clarence W. Fox* of Saugus, Mass., November 21, 1893, No. 509,154.

(29) United States Patents were granted for compression suppository molds to the following between 1889-1896:
Mayne J. Hull of Alexandria, Dakota Territory, April 23, 1889, No. 401,838;
Enos L. Cushing of Albion, N. Y., March 10, 1891, No. 448,133;
Henry C. Archibald and *James F. Snediker,* l.c.;
Frederick E. Howarth of Utica, N. Y., October 6, 1891, No. 460,620;
Clarence W. Fox, l.c.;
Charles A. Tatum and assignor Whitall, Tatum and Company of New York, N. Y., March 26, 1895, No. 536,240;
David Genese of Baltimore, Md., June 25, 1895, No. 541,529;
John G. Blount of Everett, Mass., and assignor Clarence W. Fox of Saugus, Mass., October 20, 1896, No. 569,985.

(30) Coblentz, V., *Tablets, Tablet Triturates and Compressed Suppositories,* Whitall, Tatum and Company, New York, 1897. The Whitall Tatum mold is now sold by the Armstrong Cork Company of Lancaster, Pa.

(31) United States Patent issued to:
Charles L. Trusler, Indianapolis, Indiana, April 6, 1897, No. 580,021.

(32) Wyeth, John, *Suppositories, Rectal, Vaginal, Urethral,* Phila. 20 pp. 1886. Wyeth advertised manufactured suppositories to the profession through medical journals as early as 1870.

(33) Wellcome, H. S., *Proc. Amer. Pharm. Assoc., 41,* 103 (1893).

(34) Bird, J. C., *J. Amer. Pharm. Assoc., 26,* 475 (1937); *Drug and Cosmetic Industry, 54,* 403 (1944); and Hassler, W. H. and G. J. Sperandio, *J. Amer. Pharm. Assoc., Pract. Ed., 14, 26* (1953).

(35) Gross, H. M. and C. H. Becker, *J. Amer. Pharm. Assoc., Sci. Ed., 42,* 90 (1953).

SELECTED ABSTRACTS

A Clinical Evaluation of Phenylbutazone in Rheumatoid Arthritis. Patterson, R. M., Benson, J. F., and Schoenberg, P. L. *U. S. A. F. Med. J. 4*:109 (1953). In an evaluation of the clinical effect of phenylbutazone (butazolidin) in rheumatoid arthritis, the authors selected 20 patients with a diagnosis of peripheral rheumatoid arthritis, 4 with spondylitis, and 8 with spondylitis with peripheral joint involvement. The patients were also selected because of the marked degree of discomfort and for their lack of response to other forms of treatment. The average age of the patients was 29 years. The drug was given in a dose of 600 mg. daily for 2 or 3 weeks, in most cases.

None of the 32 patients obtained marked objective improvement or a clinical remission of the disease. Sedimentation rates were not lowered and none of the patients had more than a minimal reduction in swelling. However, the analgesic property of phenylbutazone was definitely observed. Marked to moderate relief of pain, stiffness and aching was obtained by 72 per cent of the patients. No significant toxic effects traceable directly to phenylbutazone were encountered.

The authors concluded that phenylbutazone is an excellent adjunct to the treatment of rheumatoid arthritis but that it produces no true antirheumatic effects.

The Treatment of Falciparum Malaria with Pyrimethamine. Wilson, T., and Edeson, J. F. B. *Brit. Med. J.* No. 4804:253 (1953). Pyrimethamine, 2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (Daraprim), was used in the treatment of 126 Malayan patients with acute attacks of malaria. Eighty of the patients had previously untreated falciparum malaria. Of these patients 15 were given a single dose of 50 mg. of pyrimethamine; there were 2 failures; 39 were given 100 mg. in two 50 mg. doses, there were 4 failures; and 26 patients were given 300 mg. in divided doses of 100 mg. on the first day and

50 mg. on the 4 successive days, there were 7 failures. Apart from the failures in these patients the clinical response to the drug was slow. More than 1/3 of the successfully treated patients had a persistence of fever and other symptoms for a day or two after triphozoites had disappeared from the peripheral blood. In a comparable series of 25 patients treated with a single dose of 300 mg. of chloroquine there were no failures.

Twenty-four patients with falciparum infections which had proven to be resistant to proguanil were given 100 mg. of pyrimethamine. The results with these patients were so similar to those with the patients to whom proguanil had not been given that the authors concluded that resistance to proguanil does not affect the response to pyrimethamine.

Twenty-two patients with acute vivax malaria infections were treated with either 50 or 100 mg. doses of pyrimethamine. The clearance of parasites from the peripheral blood was slow but there were no failures. The authors also reported that the fever and symptoms did not persist after trophozoites had disappeared from the peripheral blood.

As a result of this study the authors concluded that pyrimethamine is unsuitable for the treatment of acute attacks of malaria caused by Malayan strains of *P. falciparum*.

Isoniazid Therapy in Pulmonary Tuberculosis. Pitts, F. W., Miller, F. L., Dye, W. E., Tempel, C. W., and Fitzpatrick, M. J. *U. S. A. F. Med. J.* 4:1 (1953). Isoniazid was given orally to 196 patients with pulmonary tuberculosis for 120 days. The drug was given in doses of 150 or 300 mg. daily alone or combined with intramuscular injections of 2 Gm. of streptomycin every third day. The authors reported on 104 of the patients who had completed 120 days of therapy.

Preliminary observations suggested that isoniazid alone in the dosage employed is not very effective, as measured by roentgenographic evaluation, although subjective improvement was obtained in most of the patients. Drug resistant organisms appeared rapidly in a rather high precentage of these cases. However, there were no serious toxic effects from the administration of the drug. The combination of streptomycin with isoniazid appeared to markedly aug-

ment the effect and to practically eliminate the appearance of resistant organisms during the first 4 months of therapy.

The authors attempted to make a preliminary comparison of the effectiveness of this new combination with the existing combination of streptomycin and para-aminosalicylic acid, which has proven value in the treatment of pulmonary tuberculosis. The authors emphasized that only a preliminary comparison could be made and that at least another year will be required before sufficient long term data is available to make a more thorough evaluation. At present it appears that the symptomatic and roentgenographic responses are of similar magnitude but that the new combination provides a higher incidence of sputum conversion after 4 months. After 4 months there appears to be little difference in drug toxicity and the development of bacterial resistance. Isoniazid and streptomycin provides greater ease of administration and better patient acceptance because of the smaller dose and lower incidence of gastric disturbance with isoniazid as compared with PAS. Both regimen provide therapy at about the same cost to the patient.

Hexamethonium Compounds in the Treatment of Essential Hypertension During Pregnancy. Morris, N. *The Lancet I*:322 (1953). Hexamethonium compounds will lower blood pressure in most hypertensive patients for a temporary period. The author evaluated the use of these compounds in the treatment of pre-eclampsia and essential hypertension in 10 pregnant women.

Since there is definite danger involved for both the mother and the fetus, treatment with these compounds was generally reserved for those cases where the prognosis for the fetus was poor and where all the usual measures had failed. The persistent hypotension and paralytic ileus which have been observed in patients following the administration of hexamethonium compounds could also be expected to occur in pregnant cases. Even a transient hypotension, with its disturbance of uteroplacental blood-flow, might kill the fetus. Since the control of the medication is more difficult and unpredictable by oral administration the author recommended the use of intramuscular therapy. Even with intramuscular therapy the response to the drug was erratic and persisted for only 3 to 4 hours.

Although the blood pressure was usually lowered in the cases reported there was no evidence that the drug altered the course of the disease. However, no patient deteriorated and none developed eclampsia, accidental hemorrhage, or gross renal damage. It was, therefore, felt that the drug helped to stabilize the disease. There was little evidence that the prognosis for the fetus was improved. In cases where hexamethonium treatment was continued during labor there was no apparent alteration of the normal course.

It was found that hexamethonium accumulated in the fetal liquor and remained there for some time after the last dose had been given. It was thought that swallowing of some of this liquor may have produced paralytic ileus and contributed to the death of two of the newborn infants.

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*Kuhn, H. S.: Tr. Am. Acad. Ophth., p. 432, (March-April) 1951.

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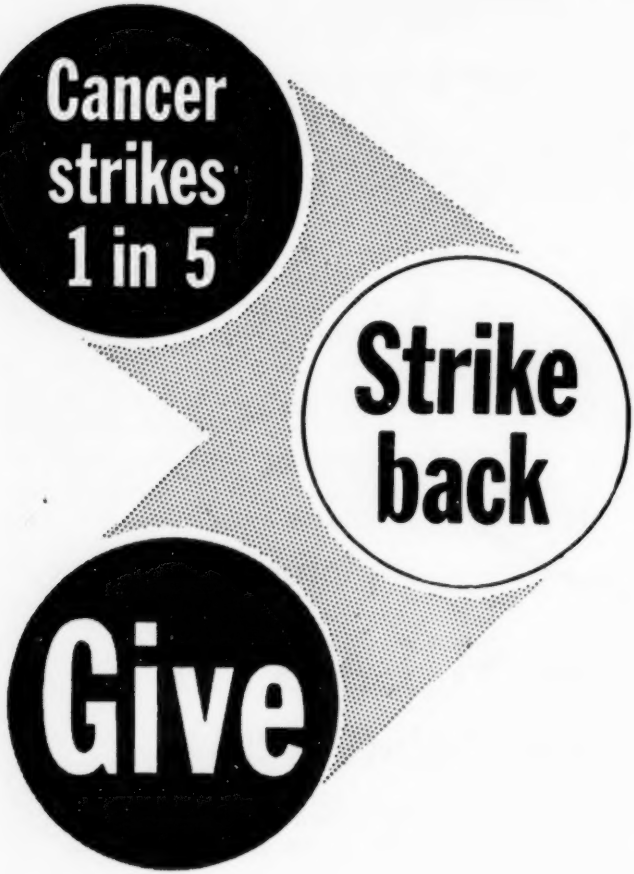

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